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Low-Dose Combination Chemotherapy for Acute Myeloid Leukemia in Elderly Patients: A Novel Approach

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Eighteen patients aged 60–84 years with acute myeloid leukemia were treated with low-dose combination chemotherapy comprising cytarabine, etoposide, and mitozantrone or 6-thioguanine; seven of these patients had a pre-existing myelodysplastic syndrome. Nine patients achieved a complete remission, and five had a partial remission. The duration of survival in these 14 responding patients has ranged from 2+ to 19+ months. Myelotoxicity occurred regularly, with time to recovery (neutrophils $\geqslant 0.5 \times 10^9$/L, platelets $\geqslant 50 \times 10^9$/L) from nadir being 10–14 days in 12 of the 14 patients. This novel approach with an overall response rate of 78% appears to be a simple and effective form of therapy for elderly patients. Am. J. Hematol. 55:115–117, 1997. © 1997 Wiley-Liss, Inc.

Key words: acute myeloid leukemia; elderly patients; low-dose combination chemotherapy

INTRODUCTION

Forty percent of patients with acute myeloid leukemia (AML) are over 65 years of age, and one-third are over age 70 [1]. Although aging is a highly individual process, elderly patients generally have delayed renal excretion of drugs and a higher incidence of treatment-related morbidity and mortality from aggressive chemotherapy comprising full-dose antileukemic drugs [2,3].

Several centres have used low-dose cytarabine (LD araC), as a single agent, and have documented a beneficial response in up to 50% of patients [4]. A randomized trial comparing LD araC and conventional intensive therapy in elderly AML patients has found more frequent early death (31% vs. 10%) and complete remission (52% vs. 32%) in the intensive therapy group, but a higher rate of partial remission (22% vs. 2%), fewer transfusion requirements, and lower number of hospital days in the LD araC therapy group. Overall survival was noted to be similar in the two groups [5]. This randomized study has highlighted the dilemma of the clinician treating elderly AML patients: whether to treat intensively to benefit a minority or to use only supportive care and LD araC to prolong survival [3]. Even with the advent of recombinant human granulocyte colony-stimulating factor, early death rate remains high (23%) and the median survival relatively short (9.2 months) in elderly patients receiving intensive induction therapy [6].

In an attempt to improve the response rate of LD araC therapy, but without the substantial toxicity associated with conventional antileukemia therapy, we designed a low-dose combination chemotherapy, including LD araC [7]. This novel approach emanated from our previous observation that the beneficial effect of LD araC therapy is due to protracted cytotoxicity in the S phase of the cell cycle [8], and the hypothesis that other antileukemic drugs, also given in low doses, may enhance the cytotoxicity without necessarily increasing the risk of complications [9]. We report here our experience of low-dose combination chemotherapy in 18 elderly AML patients.

PATIENTS AND METHODS

Eleven patients refused to receive intensive chemotherapy. The other seven were considered unsuitable for this therapy: severe surgical infection/septicemia, associated medical conditions, in six patients; social problem, in one patient. Treatment comprised LD araC, 10 mg/m^2 sc bid for 7–14 days (all patients), etoposide 100 mg/day

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TABLE I. Summary of Clinical Details

Patient	Sex/Age (yr)	Diagnosis (post)	Response to treatment†	Maintenance therapy	Duration of survival (mo)
1.	F/61	AML-M4	CR	LD ara C	12
2.	F/62	AML-M1	PR	LD ara C + TG (LD)	16
3.	M/70	AML-M4 (RAEB)	PR	Etop (LD)	13
4.	F/70	AML-M6	PR	LD ara C	10
5.	M/71	AML-M4	NR	—	3[a]
6.	M/69	AML-M4 (RAEB)	NR	—	3
7.	M/67	AML-M2	CR	Nil	14
8.	M/65	AML-M4 (CMML)	CR	Nil	14
9.	F/69	AML-M4 (RAEB)	NR	—	2
10.	F/78	AML-M7	CR	Nil	14
11.	M/74	AML-M1	CR	Nil	18
12.	M/78	AML-M4 (RAEB)	CR	Nil	13
13.	M/61	AML-M2	CR	Nil	19[b]
14.	M/84	AML-M2	NR	—	2[a]
15.	F/66	AML-M4 (CMML)	PR	Etop (LD)	12
16.	F/60	AML-M4	CR	Nil	6[b]
17.	M/60	AML-M4 (RAEB)	PR	Nil	11[b]
18.	F/67	AML-M2	CR	Nil	2[b]

AML, acute myeloblastic leukemia according to the French-American-British (FAB) classification; RAEB, refractory anaemia with excess blasts; CMML, chronic myelomonocytic leukemia; CR, complete remission (<5% blasts in bone marrow); PR, partial remission (6–15% blasts); NR, no response; LD ara C, low-dose cytarabine, TG, 6-thioguanine, LD, low dose; Etop, etoposide.

[a]Died due to sepsis during remission-induction therapy.

[b]Still alive.

PO for 7–14 days (all patients), mitozantrone 6 mg/m^2 IVI for 3 days (15 patients) or 6-thioguanine 40 mg PO bid for 7–14 days (3 patients). None received more than three courses of remission-induction therapy. The duration of therapy was determined from the results of daily blood counts and/or weekly bone marrow examinations; therapy was stopped when significant cytopenias (white blood cells $<0.5 \times 10^9$/L, platelets $<10 \times 10^9$/L) occurred or when the bone marrow examination showed significant hypoplasia. The first course of treatment was always given in the inpatient setting, but the subsequent courses required only sporadic admission during the treatment period. Patients were routinely given antibiotic prophylaxis (trimethoprim/sulfamethoxazole or ciprofloxacin and ketoconozole) and other standard supportive care measures during the cytopenic phase.

RESULTS

Table I summarises the clinical details of patients, including response to treatment and duration of survival. Complete remission (CR) was achieved in 9 of 18 patients and partial remission (PR) in 5 patients.

Treatment was well tolerated by all patients. Myelotoxicity and pancytopenia occurred regularly, with time to recovery (neutrophils $\geqslant 0.5 \times 10^9$/L, platelets $\geqslant 50 \times 10^9$/L) from nadir 10–14 days in 12 of the 14 responding patients; recovery was noted on day 22 and day 30, respectively, in the other two patients.

DISCUSSION

Although the number of patients in this study is very small, the results appear to vindicate our hypothesis. In fact, the overall response rate of 78% is better than those reported with LD araC (54%) or intensive therapy (54%) [6]. The duration of survival in the 11 responding patients has ranged from 2+ to 19+ months, with no apparent difference between the complete remission and the partial remission groups.

To the best of our knowledge, only one other study has evaluated low-dose combination chemotherapy in elderly AML patients. In the study reported by Slapak et al. [10], 29 patients were treated with LD araC for 21 days, hydroxyurea 500 mg PO bid for 22 days, and calcitriol 0.25 mg PO bid continuously; the overall response rate was 79% (CR 45%, PR 34%), and the median survival in the responding patients was 14 months. Despite differences in the design of the two studies, which were conceived and conducted independently, the striking similarities in the results should encourage further large-scale randomized studies to evaluate low-dose combination chemotherapy.

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